

These studies provide very low certainty evidence that lumbar spine bone density (measured by BMAD) increases during treatment with gender-affirming hormones in sex assigned at birth males (transfemales). Z-scores at the end of follow-up suggest average lumbar spine bone density was generally lower than in the equivalent cisgender population. The results for lumbar spine bone density (measured by BMD) were inconsistent.

Change in bone density: femoral neck

Two uncontrolled, observational, retrospective studies provided evidence relating to the effect of gender-affirming hormones on femoral neck bone density in transfemales ([Klink et al. 2015](#) and [Vlot et al. 2017](#)). See the safety results table above for a full description of the results.

These studies provide very low certainty evidence that femoral neck bone density (measured by BMAD) was unchanged in sex assigned at birth males (transfemales) during treatment with gender-affirming hormones (follow-up between 2 and 5 years). Z-scores at the end of follow-up suggest and the average femoral neck bone density was lower than in the equivalent cisgender population. The results for femoral neck bone density (measured by BMD) were inconsistent.

Change in clinical parameters: glucose, insulin and HbA1c

One uncontrolled, retrospective chart review ([Klaver et al. 2020](#)) provided evidence on glucose, insulin and HbA1c in transfemales. See the safety results table above for a full description of the results.

This study provided very low certainty evidence that gender-affirming hormones do not affect HbA1c, glucose levels, insulin levels and insulin resistance in sex assigned at birth males (transfemales) from the start of treatment to age 22 years.

Change in clinical parameters: lipids

One retrospective chart review ([Klaver et al. 2020](#)) provided evidence on the change in lipids (total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides) in transfemales. See the safety results table above for a full description of the results.

This study provides very low certainty evidence that gender-affirming hormones do not affect lipid profiles in sex assigned at birth males (transfemales) from the start of treatment to age 22 years.

Change in clinical parameters: blood pressure

One retrospective chart review ([Klaver et al. 2020](#)) provided evidence on the change in blood pressure in transfemales. See the safety results table above for a full description of the results.

This study provides very low certainty evidence that gender-affirming hormones statistically significantly increase blood pressure in sex assigned at birth males (transfemales),

	<p>although the absolute increase was small from the start of treatment to age 22 years.</p> <p>Change in clinical parameters: body mass index (BMI) One retrospective chart review (Klaver et al. 2020) provided evidence on the change in BMI in transfemales. See the safety results table above for a full description of the results.</p> <p>This study provides very low certainty evidence that gender-affirming hormones statistically significantly increase BMI in sex assigned at birth males (transfemales), although most participants were within the healthy weight range from the start of treatment to age 22 years.</p> <p>Treatment discontinuation One uncontrolled, retrospective chart review provided evidence relating to permanent or temporary discontinuation of gender-affirming hormones in transfemales (Khatchadourian et al. 2014).</p> <p>This study provides very low certainty evidence that the rates of discontinuation during treatment with gender-affirming hormones in sex assigned at birth males (transfemales) are low. Duration of treatment with gender-affirming hormones was not reported.</p> <p>Adverse effects One uncontrolled, retrospective chart review provided evidence relating to adverse effects from gender-affirming hormones in transfemales (Khatchadourian et al. 2014).</p> <p>This study provides very low certainty evidence about the potential adverse effects of gender-affirming hormones in sex assigned at birth males (transfemales). No conclusions could be drawn. Duration of treatment with gender-affirming hormones was not reported.</p>
<p>Sex assigned at birth females (transmales)</p> <p>Certainty of evidence: Very low</p>	<p>Some studies reported data separately for sex assigned at birth females (transmales). This included some direct comparisons with sex assigned at birth males (transfemales).</p> <p>Impact on mental health: depression and anxiety One uncontrolled, prospective, longitudinal study (Kuper et al. 2020) reported the change in depression (measured using QIDS clinician-reported and self-reported), anxiety and anxiety-related symptoms (measured using SCARED) in transmales. See the clinical effectiveness results above for full details.</p> <p>In Kuper et al. 2020 (n=65 to 78, varies by outcome), changes were seen in depression, anxiety and anxiety-related symptoms from baseline to follow-up but the authors did not report any statistical analysis, so it is unclear if any changes are statistically significant (VERY LOW).</p>

This study provides very low certainty evidence on the effects of gender-affirming hormones on depression, anxiety and anxiety-related symptoms over 10.9 months in transmales. No conclusions could be drawn.

Impact on mental health: suicidality

One uncontrolled, retrospective, longitudinal study ([Allen et al. 2019](#)) reported the change in Ask Suicide-Screening Questions (ASQ) in transmales compared with transfemales. See the sex assigned at birth males (transfemales) row above for full details of the results.

One uncontrolled, prospective, longitudinal study ([Achille et al. 2020](#)) reported the change in suicidal ideation in transmales measured using additional questions from the PHQ 9_Modified for Teens. See the clinical effectiveness results above for full details.

At baseline, 9.1% (3/33) of transmales had suicidal ideation, compared with 6.1% (2/33) at about 12-months follow-up (no statistical analysis reported) (**VERY LOW**).

These studies provide very low certainty evidence that any change in suicidal ideation is not different between sex assigned at birth females (transmales) and sex assigned at birth males (transfemales). Mean duration of treatment about 12 months.

Impact on quality of life

One uncontrolled, retrospective, longitudinal study ([Allen et al. 2019](#)) reported the change in the GWBS of the Paediatric Quality of Life Inventory in transmales compared with transfemales. See the sex assigned at birth males (transfemales) row above for full details of the results.

This study provides very low certainty evidence that any change in general wellbeing is not different between sex assigned at birth females (transmales) and sex assigned at birth males (transfemales). Mean duration of treatment about 12 months.

Impact on body image

One uncontrolled, prospective, longitudinal study ([Kuper et al. 2020](#)) reported change in Body Image Scale (BIS) in transmales. See the clinical effectiveness results above for full details.

In Kuper et al. 2020 (n=66), the mean (\pm SD) BIS score was 71.1 points (\pm 13.4) at baseline and 52.9 points (\pm 16.8) at follow-up (no statistical analysis reported) (**VERY LOW**).

This study provides very low certainty evidence on the effects of gender-affirming hormones on body image over 10.9 months in transmales. No conclusions could be drawn.

Change in bone density: lumbar spine

Three uncontrolled, observational, retrospective studies provided evidence relating to the effect of gender-affirming hormones on lumbar spine bone density in transmales ([Klink et al. 2015](#), [Stoffers et al. 2019](#) and [Vlot et al. 2017](#)). See the safety results table above for a full details of the results.

These studies provide very low certainty evidence that lumbar spine bone density (measured by BMAD) increases during 2 to 5 years treatment with gender-affirming hormones in sex assigned at birth females (transmales). Z-scores at the end of follow-up suggest the average lumbar spine bone density was generally lower than in the equivalent cisgender population. The results for lumbar spine bone density (measured by BMD) were inconsistent.

Change in bone density: femoral neck

Three uncontrolled, observational, retrospective studies provided evidence relating to the effect of gender-affirming hormones on femoral neck bone density in transmales ([Klink et al. 2015](#), [Stoffers et al. 2019](#) and [Vlot et al. 2017](#)). See the safety results table above for a full details of the results.

These studies provide very low certainty evidence that femoral neck bone density (measured by BMAD) statistically significantly increased in sex assigned at birth females (transmales) during 2 to 5 years treatment with gender-affirming hormones. Z-scores at the end of follow-up suggest the average femoral neck bone density was generally lower than in the equivalent cisgender population. The results for femoral neck bone density (measured by BMD) were inconsistent.

Change in clinical parameters: glucose, insulin and HbA1c

Two uncontrolled, retrospective chart reviews ([Klaver et al. 2020](#); [Stoffers et al. 2019](#)) provided evidence on glucose, insulin and HbA1c in transmales. See the safety results table above for full details of the results.

This study provided very low certainty evidence that gender-affirming hormones do not affect HbA1c, glucose levels, insulin levels and insulin resistance in sex assigned at birth females (transmales). Reported from start of treatment to age 22 years.

Change in clinical parameters: lipids

One retrospective chart review ([Klaver et al. 2020](#)) provided evidence on the change in lipids (total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides) in transmales. See the safety results table above for full details of the results.

This study provides very low certainty evidence that treatment with gender-affirming hormones is associated with a small but statistically significant worsening of cholesterol levels in sex assigned at birth females (transmales), but mean cholesterol and triglyceride levels were within the UK reference range at end of treatment, from start of treatment to age 22 years.

Change in clinical parameters: blood pressure

One retrospective chart review ([Klaver et al. 2020](#)) provided evidence on the change in blood pressure in transmales. See the safety results table above for full details of the results.

	<p>This study provides very low certainty evidence that gender-affirming hormones statistically significantly increase blood pressure in sex assigned at birth females (transmales), although the absolute increase was small, from start of treatment to age 22 years.</p> <p>Change in clinical parameters: body mass index (BMI) One retrospective chart review (Klaver et al. 2020) provided evidence on the change in body mass index (BMI) in transmales. See the safety results table above for full details of the results.</p> <p>This study provides very low certainty evidence that gender-affirming hormones statistically significantly increase BMI in sex assigned at birth females (transmales), although most participants were within the healthy weight range, from start of treatment to age 22 years.</p> <p>Change in clinical parameters: liver function One retrospective chart review (Stoffers et al. 2019) provided non-comparative evidence on the change in liver enzymes in transmales between starting gender-affirming hormones and up to 24-months follow-up. See the safety results table above for full details of the results.</p> <p>This study provides very low certainty evidence that gender-affirming hormones for about 12 months do not affect liver function in sex assigned at birth females (transmales).</p> <p>Change in clinical parameters: kidney function One retrospective chart review (Stoffers et al. 2019) provided non-comparative evidence on the change in serum creatinine and serum urea levels in transmales between starting gender-affirming hormones and up to 24-months follow-up. See the safety results table above for full details of the results.</p> <p>This study provides very low certainty evidence on the effects of gender-affirming hormones on kidney function in sex assigned at birth females (transmales). A statistically significant increase in creatinine levels was seen at about 12 months follow-up, but these were within the UK reference range. Urea levels were unchanged.</p> <p>Treatment discontinuation One uncontrolled, retrospective chart review provided evidence relating to permanent or temporary discontinuation of gender-affirming hormones in transmales (Khatchadourian et al. 2014). See the safety results table above for full details of the results.</p> <p>This study provides very low certainty evidence that the rates of treatment discontinuation with gender-affirming hormones in sex assigned at birth females (transmales) is low. Duration of gender-affirming hormones not reported.</p> <p>Adverse effects</p>
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	<p>One uncontrolled, retrospective chart review provided evidence for adverse effects from gender-affirming hormones in transmales (Khatchadourian et al. 2014). See the safety results table above for full details of the results.</p> <p>This study provides very low certainty evidence about the potential adverse effects of gender-affirming hormones in sex assigned at birth females (transmales). No conclusions could be drawn. Duration of gender-affirming hormones not reported.</p>
Duration of gender dysphoria	No evidence was identified.
Age at onset of gender dysphoria	No evidence was identified.
Age at onset of puberty	No evidence was identified.
Tanner stage at which GnRH analogue or gender-affirming hormones started	One uncontrolled, prospective, longitudinal study (Kuper et al. 2020) reported the impact of Tanner stage on outcomes, although it is not clear whether this is referring to Tanner stage at initial assessment, at the start of GnRH analogues or at another timepoint.
Diagnosis of autistic spectrum disorder	No evidence was identified.
Diagnosis of a mental health condition	<p>One uncontrolled, prospective, longitudinal study (Achille et al. 2020) reported outcomes that were adjusted for engagement in counselling and medicines for mental health problems. Information about diagnoses and treatment were not provided. Rates of mental health issues appear to be high in the cohort.</p> <p>Impact on mental health</p> <p>Achille et al. 2020 reported the change in depression scores, controlled for engagement in counselling and medicines for mental health problems (measured using the Center for Epidemiologic Studies Depression [CESD-R] scale and Patient Health Questionnaire Modified for Teens [PHQ 9_Modified for Teens] score:</p> <ul style="list-style-type: none"> • There was no statistically significant change in CESD-R from baseline to about 12-months follow-up. • There was no statistically significant change in PHQ 9_Modified for Teens score from baseline to about 12-months follow-up (VERY LOW). <p>Impact on quality of life</p> <p>Achille et al. 2020 reported the change in quality of life scores, controlled for engagement in counselling and medicines for mental health problems (measured using the Quality of Life Enjoyment and Satisfaction Questionnaire [QLES-Q-SF] score:</p> <ul style="list-style-type: none"> • There was no statistically significant change in QLES-Q-SF score from baseline to about 12-months follow-up (VERY LOW). <p>This study provides very low certainty evidence about outcomes that were adjusted for engagement in counselling and medicines for mental health problems. No conclusions could be drawn.</p>

Abbreviations: ASQ: Ask Suicide-Screening Questions; CESD-R: Center for Epidemiologic Studies Depression; GnRH: Gonadotrophin releasing hormone; GWBS: General Well-Being

Scale; HDL: high-density lipoproteins; LDL: low-density lipoproteins; p: p-value; PHQ 9_Modified for Teens: Patient Health Questionnaire Modified for Teens; QLES-Q-SF: Quality of Life Enjoyment and Satisfaction Questionnaire.

From the evidence selected,

- (a) **what are the criteria used by the research studies to define gender dysphoria, gender identity disorder and gender incongruence of childhood?**
- (b) **what were the ages at which participants commenced treatment with gender-affirming hormones?**
- (c) **what was the duration of treatment with GnRH analogues?**

Outcome	Evidence statement																		
Diagnostic criteria	<p>The DSM-IV-TR criteria was used in 3 studies (Klaver et al. 2020, Klink et al. 2015 and Vlot et al. 2017).</p> <p>The DSM-V criteria was used in 2 studies (Kuper et al. 2020 and Stoffers et al. 2019). The DSM-V has one overarching definition of gender dysphoria with separate specific criteria for children and for adolescents and adults. The general definition describes a conflict associated with significant distress and/or problems functioning associated with this conflict between the way they feel and think of themselves which must have lasted at least 6 months.</p> <p>The ICD-10 diagnosis of 'transsexualism' was used in 1 study (Kaltiala et al. 2020). The authors state that this is the corresponding diagnosis to 'gender dysphoria' in the DSM-V, and that diagnostic assessments in the study location (Finland) take place according to ICD-10.</p> <p>It was not reported how gender dysphoria was defined in the remaining 4 studies (VERY LOW).</p> <p>From the evidence selected, the most commonly reported diagnostic criteria for gender dysphoria (5/10 studies) was the DSM criteria in use at the time the study was conducted.</p>																		
Age when gender-affirming hormones started	<p>8/10 studies reported the age at which participants started treatment with gender-affirming hormones, either as the mean age (with SD) or median age (with the range):</p> <table border="1"> <thead> <tr> <th>Study</th> <th>Mean age (\pm SD)</th> </tr> </thead> <tbody> <tr> <td>Allen et al. 2019</td> <td>16.7 years (not reported)</td> </tr> <tr> <td>Khatchadourian et al. 2014</td> <td>17.4 years (1.9)</td> </tr> <tr> <td>Klaver et al. 2020</td> <td>16.4 years (1.1) in transfemales 16.9 years (0.9) in transmales</td> </tr> <tr> <td>Kuper et al. 2020</td> <td>16.2 (1.2)</td> </tr> <tr> <td>Klink et al. 2015</td> <td>16.6 years (1.4) in transfemales 16.4 years (2.3) in transmales</td> </tr> </tbody> </table> <table border="1"> <thead> <tr> <th>Study</th> <th>Median age (range)</th> </tr> </thead> <tbody> <tr> <td>Stoffers et al. 2019</td> <td>17.2 years (15 to 19.5)</td> </tr> <tr> <td>Vlot et al. 2017</td> <td>16.3 years (15.9 to 19.5) in transfemales 16.0 years (14.0 to 18.9) in transmales</td> </tr> </tbody> </table>	Study	Mean age (\pm SD)	Allen et al. 2019	16.7 years (not reported)	Khatchadourian et al. 2014	17.4 years (1.9)	Klaver et al. 2020	16.4 years (1.1) in transfemales 16.9 years (0.9) in transmales	Kuper et al. 2020	16.2 (1.2)	Klink et al. 2015	16.6 years (1.4) in transfemales 16.4 years (2.3) in transmales	Study	Median age (range)	Stoffers et al. 2019	17.2 years (15 to 19.5)	Vlot et al. 2017	16.3 years (15.9 to 19.5) in transfemales 16.0 years (14.0 to 18.9) in transmales
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	<p>Age at the start of treatment was not reported in 3 studies:</p> <ul style="list-style-type: none"> • In Achille et al. 2020 the mean age at initial assessment (baseline) was 16.2 years (SD ±2.2) • In Kaltiala et al. 2020 the mean age at diagnosis was 18.1 years (range 15.2 to 19.9) • In Lopez de Lara et al. 2020 the mean age of participants was 16 years (range 14 to 18), although it is not clear if this is at the initial assessment or at the start of gender-affirming hormones. <p>The evidence included showed that most children and adolescents started treatment with gender-affirming hormones at about 16 to 17 years, with a range of about 14 to 19 years.</p>								
<p>Duration of treatment with GnRH analogues</p>	<p>The duration of treatment with GnRH analogues was reported in 3/10 studies:</p> <table border="1" data-bbox="526 701 1367 928"> <thead> <tr> <th>Study</th> <th>Median duration</th> </tr> </thead> <tbody> <tr> <td>Klaver et al. 2020</td> <td>2.1 years (IQR 1.0 to 2.7) in transfemales 1.0 years (IQR 0.5 to 2.9) in transmales</td> </tr> <tr> <td>Klink et al. 2015</td> <td>1.3 years (range 0.5 to 3.8) in transfemales 1.5 years (range 0.25 to 5.2) in transmales (GnRH analogue monotherapy)</td> </tr> <tr> <td>Stoffers et al. 2019</td> <td>8 months (range 3 to 39)</td> </tr> </tbody> </table> <p>The evidence included showed wide variation in the duration of treatment with gender-affirming hormones, but most studies did not report this information. Treatment duration ranged from a few months up to about 5 years.</p>	Study	Median duration	Klaver et al. 2020	2.1 years (IQR 1.0 to 2.7) in transfemales 1.0 years (IQR 0.5 to 2.9) in transmales	Klink et al. 2015	1.3 years (range 0.5 to 3.8) in transfemales 1.5 years (range 0.25 to 5.2) in transmales (GnRH analogue monotherapy)	Stoffers et al. 2019	8 months (range 3 to 39)
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Abbreviations: DSM, Diagnostic and Statistical Manual of Mental Disorders criteria; GnRH, Gonadotrophin-releasing hormone; ICD, International Statistical Classification of Diseases and Related Health Problems; IQR, interquartile range; SD, standard deviation.

6. Discussion

A key limitation to identifying the effectiveness and safety of gender-affirming hormones for children and adolescents with gender dysphoria is the lack of reliable comparative studies. All the studies included in this evidence review are uncontrolled observational studies, which are subject to bias and confounding and were of very low certainty using modified GRADE. The size of the population with gender dysphoria means conducting a prospective trial may be unrealistic, at least on a single centre basis. There may also be ethical issues with a 'no treatment arm' in comparative trials of gender-affirming hormones, where there may be poor mental health outcomes if treatment is withheld. However, the use of an active comparator such as close psychological support may reduce ethical concerns in future trials. A fundamental limitation of all the uncontrolled studies included in this review is that any changes in scores from baseline to follow-up could be attributed to a regression-to-the-mean.

The included studies have relatively short follow-up, with an average duration of treatment with gender-affirming hormones between around 1 year and 5.8 years. Further studies with a

longer follow-up are needed to determine the long-term effect of gender-affirming hormones for children and adolescents with gender dysphoria.

Most studies included in this review did not report comorbidities (physical or mental health) and no study reported concomitant treatments in detail. Because of this it is not clear whether any changes observed were due to gender-affirming hormones or other treatments the participants may have received. For example, we do not know if any improvement in depression symptom score over time was the result of gender-affirming hormones or the mental health support the person may be receiving (including medicines or counselling). This may be of particular importance for the mental health outcomes discussed in this review, since depression, anxiety and other related symptoms are common in children and adolescents with gender dysphoria. In [Achille et al. 2020](#), at baseline around one-third of participants were taking medicines for mental health problems and around two-thirds reported being depressed in the past year. In [Kaltiala et al. 2020](#), half the participants needed mental health treatment during and before gender identity assessment, with the most common reasons for treatment being depression, anxiety and suicidality. Only 1 study reported outcomes adjusted for engagement in counselling and medicines for mental health problems (Achille et al. 2020). This study found that gender-affirming hormones had no significant impact on depression and quality of life when adjusted for mental health care, despite significant improvements reported for the unadjusted results. However, it is not possible to draw conclusions on the impact of concurrent mental health treatment on the effect of gender-affirming hormones based on this study alone. Details of the mental health care provided are not reported in the study and results are presented for transfemales and transmales separately, resulting in small patient numbers and possible underpowering.

In most of the included studies, details of the gender-affirming hormone treatment regimens are poorly reported, with limited information provided about the medicines, doses and routes of administration used. It is not clear whether the interventions used in the studies are reflective of current UK practice for children and adolescents with gender dysphoria. There is also the suggestion that the hormone dose used in 1 study may have been too low; the authors of [Klink et al. 2015](#) suggest that the relatively low initial dose of oestrogen for transfemales may be the reason for the observed lack of effect on lumbar spine bone density. Duration of treatment with a GnRH analogue is also poorly reported and is only stated in 3/10 studies.

There is a degree of indirectness in some studies, with some participants included that fall outside of the population of this evidence review. For example, in [Kuper et al. 2020](#) 17% of participants received puberty suppression alone, and in Achille et al. 2020, 30% of participants received no treatment or puberty suppression alone. Some results and statistical analyses are only reported for the whole cohort in these studies and not the subgroup of participants who received gender-affirming hormones.

Participant numbers are poorly reported in some of the included studies. In [Achille et al. 2020](#), 47% (45/95) of the people who entered the study did not have follow-up data and were excluded from the analyses, with no explanation or description of those people lost to follow-up. In Kuper et al. 2020, the number of participants varied by outcome, with less than two-thirds of participants providing data for some outcomes. The authors provide no explanation for this incomplete reporting.

It is not clear whether some outcome measures, specifically those related to psychosocial functioning, are relevant to the UK population. In Kaltiala et al. 2020, an observational study conducted in Finland, the proportion of participants living with parents or guardians is reported as marker of appropriate functioning. The authors state that in Finnish culture young people tend to leave the parental home early, with only around one-quarter of 20 to 24 year olds still living at home. This is lower than in the UK, where around half of 20 to 24 year olds live with their parents or guardians ([ONS: Why are more young people living with their parents?](#)).

It is difficult to draw firm conclusions for many of the effectiveness and safety outcomes reported in the included studies because many different scoring tools and methods were used to assess the same outcome, often with conflicting results. For example, bone density is reported as bone mineral density (BMD) and bone mineral apparent density (BMAD) in the same study, the latter being a size-adjusted measure often useful for people whose bones are still growing. For some populations (transfemale versus transmale) and bone regions (lumber spine versus femoral neck), statistically significant differences in BMD are reported but not for BMAD, and vice versa.

In addition to this, most outcomes reported across the included studies do not have an accepted minimal clinically important difference (MCID), making it difficult to determine whether any observed statistically significant changes are clinically meaningful. However, the authors of some studies report thresholds to interpret the results of the scoring tools, so some conclusions can be made. For example, the mean Utrecht Gender Dysphoria Scale (UGDS) score (a measure of gender dysphoria symptoms) reduced to about 15 points after treatment with gender-affirming hormones ([Lopez de Lara et al. 2020](#)). The authors state that scores of 40 points or above signify gender dysphoria, suggesting that after about 12 months of treatment with gender-affirming hormones, the majority of participants did not have symptoms of gender dysphoria.

The impact of gender-affirming hormones on bone density was reported in 3 studies (Klink et al. 2015, [Stoffers et al. 2019](#) and [Vlot et al. 2017](#)). Although these studies did not include a control group, comparisons to a reference population are reported using z-scores. Comparisons were made to a cisgender population, meaning for example that bone density in transfemales was compared with bone density in cisgender males. The authors of Klink et al. 2015 note that this may not be the ideal comparison, because androgens and oestrogens affect bone differently, and that bone properties in a trans population differ from their age- and sex assigned at birth-matched controls. Beyond this, a major limitation when trying to determine the impact of gender-affirming hormones on the short- and long-term bone health of children and adolescents is the lack of data on fracture rates and other patient-orientated outcomes, including rates of osteoporosis. Studies of GnRH analogues in children and adolescents with gender dysphoria suggest that GnRH analogue treatment may reduce the expected increase in bone density (which is expected during puberty). Although improvements in bone density were reported following treatment with gender-affirming hormones, Z-scores suggest that bone density remained lower in transfemales and transmales compared with an equivalent cisgender population.

One study reported on cardiovascular risk factors at age 22 years in people who started gender-affirming hormones for gender dysphoria as adolescents. While glucose levels, insulin levels and insulin resistance were broadly unchanged at 22 years, statistically

significant increases in blood pressure and body mass index were seen. A small but statistically significant worsening of the lipid profile in transmales who received testosterone was also seen at age 22 years. However, further studies with a considerably longer follow-up and a focus on patient-oriented outcomes, including cardiovascular events and mortality are needed to determine the long-term impact on cardiovascular health of starting gender-affirming hormones during childhood and adolescence.

Only 1 study reported adverse events and discontinuation rates with gender-affirming hormones in children and adolescents. Conclusions on these outcomes cannot be made based on this study alone.

This review did not identify sub-groups of people who may benefit more from gender-affirming hormones. Limited evidence from 2 studies suggests there was no difference in response to treatment between transfemales and transmales for mental health and quality of life (Achille et al. 2020 and [Allen et al. 2019](#)).

7. Conclusion

This evidence review found limited evidence for the effectiveness and safety of gender-affirming hormones in children and adolescents with gender dysphoria, with all studies being uncontrolled, observational studies, and all outcomes of very low certainty. Any potential benefits of treatment must be weighed against the largely unknown long-term safety profile of these treatments.

The results from 5 uncontrolled, observational studies ([Achille et al. 2020](#), [Allen et al. 2019](#), [Kaltiala et al. 2020](#), [Kuper et al. 2020](#), [Lopez de Lara et al. 2020](#)) suggest that, in children and adolescents with gender dysphoria, gender-affirming hormones are likely to improve symptoms of gender dysphoria, and may also improve depression, anxiety, quality of life, suicidality, and psychosocial functioning. The impact of treatment on body image is unclear. All results were of very low certainty. The clinical relevance of any improvements to the person is difficult to determine because most outcomes do not have a recognised minimal clinically important difference, and the authors do not present statistical analysis for some outcomes.

A further 5 uncontrolled, observational studies ([Khatchadourian et al. 2014](#), [Klaver et al. 2020](#), [Klink et al. 2015](#), [Stoffers et al. 2019](#) and [Vlot et al. 2017](#)) reported on safety outcomes, all of which provided very low certainty evidence. Statistically significant increases in some measures of bone density were seen following treatment with gender-affirming hormones, although results varied by bone region (lumber spine versus femoral neck) and by population (transfemales versus transmales). However, z-scores suggest that bone density remained lower in transfemales and transmales compared with an equivalent cisgender population. Results from 1 study of gender-affirming hormones started during adolescence reported statistically significant increases in blood pressure and body mass index, and worsening of the lipid profile (in transmales) at age 22 years, although longer term studies that report on cardiovascular event rates are needed. Adverse events and discontinuation rates associated with gender-affirming hormones were only reported in 1 study, and no conclusions can be made on these outcomes.

This review did not identify sub-groups of people who may benefit more from gender-affirming hormones. Limited evidence from 2 studies suggests there was no difference in

response to treatment between transfemales and transmales for mental health and quality of life (Achille et al. 2020 and Allen et al. 2019).

No cost-effectiveness evidence was found to determine whether gender-affirming hormones are a cost-effective treatment for children and adolescents with gender dysphoria.

Appendix A PICO

The review questions for this evidence review are:

1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?
2. For children and adolescents with gender dysphoria, what is the short-term and long-term safety of gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?
3. For children and adolescents with gender dysphoria, what is the cost-effectiveness of gender-affirming hormones compared to one or a combination of psychological support, social transitioning to the desired gender or no intervention?
4. From the evidence selected, are there particular sub-groups of children and adolescents with gender dysphoria that derive comparatively more (or less) benefit from treatment with gender-affirming hormones than the wider population of children and adolescents with gender dysphoria?
5. From the evidence selected,
 - (a) what are the criteria used by the research studies to define gender dysphoria, gender identity disorder and gender incongruence of childhood?
 - (b) what were the ages at which participants commenced treatment with gender-affirming hormones?
 - (c) what was the duration of GnRH analogues treatment?

PICO table

P –Population and Indication	<p>Children and adolescents aged 18 years or less who have gender dysphoria, gender identity disorder or gender incongruence of childhood as defined by the study.</p> <p>The following subgroups of children and adolescents with gender dysphoria, gender identity disorder or gender incongruence of childhood need to be considered:</p> <ul style="list-style-type: none"> • Sex assigned at birth males • Sex assigned at birth females
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	<ul style="list-style-type: none"> • The duration of gender dysphoria: less than 6 months, 6-24 months, and more than 24 months) • The age at which treatment was initiated with GnRH analogues and with gender-affirming hormones. • The age of onset of gender dysphoria • The age of onset of puberty • Adolescents with gender dysphoria who have a pre-existing diagnosis of autistic spectrum disorder. • Adolescents with gender dysphoria who had a significant mental health symptom load at diagnosis including anxiety, depression (with or without a history of self-harm and suicidality), psychosis, personality disorder, Attention Deficit Hyperactivity Disorder and eating disorders.
<p>I – Intervention</p>	<p>Gender-affirming hormone treatments:</p> <ul style="list-style-type: none"> • A testosterone preparation for sex assigned at birth female patients which may include testosterone in the form of Sustanon injections*; testosterone enantate injections; Tostran gel*; Testogel; Testim gel; oral testosterone capsules in the form of testosterone undecanoate (Restandol); Andriol testocaps; Nebido • An oestradiol preparation** for sex assigned at birth male patients which may include: oral estradiol valerate*; oestrogen patches (7β-oestradiol patches e.g. Evorel or Estradem); Estradot patches; ethinyloestradiol *** <p>*These are the used by Leeds Hospital, England. ** Be aware that the American spelling is oestrogen without the ‘o’. ***Ethinyloestradiol is rarely used.</p>
<p>C – Comparator(s)</p>	<p>One or a combination of:</p> <ul style="list-style-type: none"> • Psychological support • Social transitioning to the gender with which the individual identifies. <p>No intervention</p>
<p>O – Outcomes</p>	<p>There are no known minimal clinically important differences and there are no preferred timepoints for the outcome measures selected.</p> <p>All outcomes should be stratified by:</p> <ul style="list-style-type: none"> • The age at which treatment with gender-affirming hormones was initiated • The length of treatment with GnRH analogues where possible. <p><u>A: Clinical Effectiveness</u></p> <p><i>Critical to decision making</i></p> <ul style="list-style-type: none"> • Impact on gender dysphoria <p>This outcome is critical because gender dysphoria in adolescents and children is associated with significant distress and problems functioning. Impact on gender dysphoria may be measured by the Utrecht Gender</p>

	<p>Dysphoria Scale. Other measures as reported in studies may be used as an alternative to the stated measure.</p> <ul style="list-style-type: none"> <p>• Impact on mental health</p> <p>Examples of mental health problems include self-harm, thoughts of suicide, suicide attempts, suicide, eating disorders, depression/low mood and anxiety. These outcomes are critical because self-harm and thoughts of suicide have the potential to result in significant physical harm and for completed suicides the death of the young person. Disordered eating habits may cause significant morbidity in young people. Depression and anxiety are also critical outcomes because they may impact on social, occupational, or other areas of functioning of children and adolescents. The Child and Adolescent Psychiatric Assessment (CAPA) may be used to measure depression and anxiety. The impact on self-harm and suicidality (ideation and behaviour) may be measured using the Suicide Ideation Questionnaire Junior. Other measures may be used as an alternative to the stated measure.</p> <p>• Impact on Quality of Life</p> <p>This outcome is critical because gender dysphoria in children and adolescents may be associated with a significant reduction in health-related quality of life. Quality of Life may be measured by the KINDL questionnaire, Kidscreen 52.</p> <p>Other measures as reported in studies may be used as an alternative to the stated measures.</p> <p><i>Important to decision making</i></p> <p>• Impact on body image</p> <p>This outcome is important because some young people with gender dysphoria may desire to take steps to suppress features of their physical appearance associated with their sex assigned at birth or accentuate physical features of their experienced gender. The Body Image Scale could be used as a measure. Other measures as reported in studies may also be used as an alternative to the stated measure.</p> <p>• Psychosocial Impact</p> <p>Examples of psychosocial impact are: coping mechanisms which may impact on substance misuse; family relationships; peer relationships. This outcome is important because gender dysphoria in adolescents and children is associated with internalising and externalising behaviours and emotional and behavioural problems which may impact on social and occupational functioning. The child behavioural check list (CBCL) may be used to measure the impact on psychosocial functioning. Other measures as reported in studies may be used as an alternative to the stated measure.</p> <p>• Engagement with health care services</p> <p>This outcome is important because patient engagement with healthcare services will impact on their clinical outcomes. Engagement with health care services may be measured using the Youth Health Care measure-satisfaction, utilization, and needs (YHC-SUN) questionnaire. Loss to follow up and should also be ascertained as part of this outcome.</p>
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	<p>Alternative measures to the YHC-SUN questionnaire may be used as reported in studies.</p> <ul style="list-style-type: none"> • Transitioning surgery - Impact on extent of and satisfaction with surgery This outcome is important because some children and adolescents with gender dysphoria may in adulthood proceed to transitioning surgery. Stated measures of the extent of surgery and satisfaction with surgery in studies may be reported. • De-transition The proportion of patients who de-transition following the commencement of gender-affirming hormone treatment and the reasons why. This outcome is important to patients because there is uncertainty about the short and long term safety and adverse effects of gender-affirming hormones in children and adolescents with gender dysphoria. <p><u>B: Safety</u></p> <ul style="list-style-type: none"> • Short and long -term safety and adverse effects of taking gender-affirming hormones is important to assess whether treatment causes acute side effects that may lead to withdrawing the treatment or long term effects that may impact on decisions for transitioning or de-transitioning. <p>Aspects to be reported on should include Impact of the drug use such as clinically relevant derangement in renal and liver function tests, lipids, glucose, insulin and glycosylated haemoglobin, cognitive development and functioning.</p> <p>The clinical and physical impact of temporary and permanent withdrawal the drug such as when patients decide to de-transition – e.g. delay in the attainment of peak bone mass, attenuation of peak bone mass, permanent physical effects.</p> <p><u>C: Cost effectiveness</u></p> <p>Cost effectiveness studies should be reported.</p>
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	18 years or less
Date limits	2000-2020

Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, guidelines and pre-publication prints
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase, the Cochrane Library, HTA and APA PsycInfo were searched on 21 July 2020, limiting the search to papers published in English language in the last 20 years. Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, guidelines, pre-publication prints, case reports and resource utilisation studies were excluded.

Database: Medline

Platform: Ovid

Version: Ovid MEDLINE(R) <1946 to July 17, 2020>

Search date: 21 Jul 2020

Number of results retrieved: 650

Search strategy:

Database: Ovid MEDLINE(R) <1946 to July 17, 2020>

Search Strategy:

-
- 1 Gender Dysphoria/ (485)
 - 2 Gender Identity/ (18431)
 - 3 "Sexual and Gender Disorders"/ (75)
 - 4 Transsexualism/ (3758)
 - 5 Transgender Persons/ (3134)
 - 6 Health Services for Transgender Persons/ (136)
 - 7 exp Sex Reassignment Procedures/ (835)
 - 8 (gender* adj3 (dysphori* or incongru* or identi* or disorder* or confus* or minorit* or queer*)).tw. (7223)
 - 9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (12665)
 - 10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (102312)
 - 11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (6969)
 - 12 (male-to-female or m2f or female-to-male or f2m).tw. (114785)
 - 13 or/1-12 (252562)
 - 14 exp Infant/ or Infant Health/ or Infant Welfare/ (1137237)
 - 15 (prematu* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (852126)
 - 16 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (1912796)
 - 17 Minors/ (2572)
 - 18 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (2360626)
 - 19 exp pediatrics/ (58102)
 - 20 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (835833)
 - 21 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (2023650)
 - 22 Puberty/ (13277)

23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert*
or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn.
(424041)

24 Schools/ (38087)

25 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (7199)

26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or
pupil* or student*).ti,ab,jn. (468784)

27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen"
or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or
aged)).ti,ab. (89314)

28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19")
adj2 (year or years or age or ages or aged)).ti,ab. (887443)

29 or/14-28 (5532185)

30 13 and 29 (79220)

31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw.
(7)

32 30 or 31 (79220)

33 Hormones/ad, tu, th (4514)

34 exp Progesterone/ad, tu, th (10899)

35 exp Estrogens/ad, tu, th (28936)

36 exp Gonadal Steroid Hormones/ad, tu, th (34137)

37 (progesteron* or oestrogen* or estrogen*).tw. (196074)

38 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or
treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)).tw. (544)

39 exp Estradiol/ad, tu, th (10823)

40 exp Testosterone/ad, tu, th (8318)

41 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or
testocaps* or nebido or testavan).tw. (74936)

42 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylesttrad* or elleste or
progynova or zumenon or bedol or femseven or nuvelle).tw. (90464)

43 or/33-42 (304239)

44 32 and 43 (3183)

45 limit 44 to yr="2000 -Current" (2019)

46 animals/ not humans/ (4685420)

47 45 not 46 (1194)

48 limit 47 to english language (1155)

49 (MEDLINE or pubmed).tw. (163678)

50 systematic review.tw. (121198)

51 systematic review.pt. (130231)

52 meta-analysis.pt. (117148)

53 intervention\$.ti. (123904)

54 or/49-53 (380217)

55 randomized controlled trial.pt. (509468)

56 randomi?ed.mp. (796957)

57 placebo.mp. (194937)

58 or/55-57 (848627)

59 exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation
studies as topic/ or exp statistics as topic/ (5562241)

60 ((control and (group* or study)) or (time and factors)).mp. (3274107)

61 (program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-
up*).mp. (4624419)

62 or/59-61 (9030680)

63 Observational Studies as Topic/ (5177)

64 Observational Study/ (81866)

65 Epidemiologic Studies/ (8358)

- 66 exp Case-Control Studies/ (1090891)
- 67 exp Cohort Studies/ (2011414)
- 68 Cross-Sectional Studies/ (332273)
- 69 Controlled Before-After Studies/ (526)
- 70 Historically Controlled Study/ (185)
- 71 Interrupted Time Series Analysis/ (913)
- 72 Comparative Study.pt. (1866044)
- 73 case control\$.tw. (112152)
- 74 case series.tw. (59119)
- 75 (cohort adj (study or studies)).tw. (170281)
- 76 cohort analy\$.tw. (6758)
- 77 (follow up adj (study or studies)).tw. (45131)
- 78 (observational adj (study or studies)).tw. (86247)
- 79 longitudinal.tw. (204239)
- 80 prospective.tw. (495367)
- 81 retrospective.tw. (442876)
- 82 cross sectional.tw. (284856)
- 83 or/63-82 (4368140)
- 84 54 or 58 or 62 or 83 (9402123)
- 85 48 and 84 (683)
- 86 limit 85 to (letter or historical article or comment or editorial or news or case reports)
- (33)
- 87 85 not 86 (650)

Database: Medline in-process

Platform: Ovid

Version: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to July 17, 2020>

Search date: 21 July 2020

Number of results retrieved: 122

Search strategy:

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to July 17, 2020>

Search Strategy:

-
- 1 Gender Dysphoria/ (0)
 - 2 Gender Identity/ (0)
 - 3 "Sexual and Gender Disorders"/ (0)
 - 4 Transsexualism/ (0)
 - 5 Transgender Persons/ (0)
 - 6 Health Services for Transgender Persons/ (0)
 - 7 exp Sex Reassignment Procedures/ (0)
 - 8 (gender* adj3 (dysphori* or incongru* or identi* or disorder* or confus* or minorit* or queer*)).tw. (1473)
 - 9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (2315)
 - 10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (20821)
 - 11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (963)
 - 12 (male-to-female or m2f or female-to-male or f2m).tw. (15453)
 - 13 or/1-12 (39735)
 - 14 exp Infant/ or Infant Health/ or Infant Welfare/ (0)
 - 15 (prematu* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (80295)

16 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (0)
 17 Minors/ (0)
 18 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (320315)
 19 exp pediatrics/ (0)
 20 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (119124)
 21 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (0)
 22 Puberty/ (0)
 23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert*
 or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn.
 (59969)
 24 Schools/ (0)
 25 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (0)
 26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or
 pupil* or student*).ti,ab,jn. (68979)
 27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen"
 or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or
 aged)).ti,ab. (10287)
 28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19")
 adj2 (year or years or age or ages or aged)).ti,ab. (112220)
 29 or/14-28 (523053)
 30 13 and 29 (9143)
 31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw.
 (3)
 32 30 or 31 (9144)
 33 Hormones/ad, tu, th (0)
 34 exp Progesterone/ad, tu, th (0)
 35 exp Estrogens/ad, tu, th (0)
 36 exp Gonadal Steroid Hormones/ad, tu, th (0)
 37 (progesteron* or oestrogen* or estrogen*).tw. (13291)
 38 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or
 treatment* or prescri* or pharm* or medic* or drug* or intervention* or care)).tw. (241)
 39 exp Estradiol/ad, tu, th (0)
 40 exp Testosterone/ad, tu, th (0)
 41 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or
 testocaps* or nebido or testavan).tw. (5458)
 42 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylestrad* or elleste or
 progynova or zumenon or bedol or femseven or nuvelle).tw. (4772)
 43 or/33-42 (19706)
 44 32 and 43 (316)
 45 limit 44 to yr="2000 -Current" (303)
 46 animals/ not humans/ (1)
 47 45 not 46 (303)
 48 limit 47 to english language (303)
 49 (MEDLINE or pubmed).tw. (36030)
 50 systematic review.tw. (29830)
 51 systematic review.pt. (1007)
 52 meta-analysis.pt. (49)
 53 intervention\$.ti. (21354)
 54 or/49-53 (68976)
 55 randomized controlled trial.pt. (277)
 56 randomi?ed.mp. (74978)
 57 placebo.mp. (18290)
 58 or/55-57 (81427)
 59 exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation
 studies as topic/ or exp statistics as topic/ (455)

60 ((control and (group* or study)) or (time and factors)).mp. (214372)
61 (program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-
up*).mp. (339764)
62 or/59-61 (507046)
63 Observational Studies as Topic/ (0)
64 Observational Study/ (91)
65 Epidemiologic Studies/ (0)
66 exp Case-Control Studies/ (1)
67 exp Cohort Studies/ (1)
68 Cross-Sectional Studies/ (0)
69 Controlled Before-After Studies/ (0)
70 Historically Controlled Study/ (0)
71 Interrupted Time Series Analysis/ (0)
72 Comparative Study.pt. (46)
73 case control\$.tw. (14451)
74 case series.tw. (13070)
75 (cohort adj (study or studies)).tw. (29119)
76 cohort analy\$.tw. (1039)
77 (follow up adj (study or studies)).tw. (3540)
78 (observational adj (study or studies)).tw. (17421)
79 longitudinal.tw. (34485)
80 prospective.tw. (63689)
81 retrospective.tw. (73761)
82 cross sectional.tw. (60195)
83 or/63-82 (250805)
84 54 or 58 or 62 or 83 (687622)
85 48 and 84 (126)
86 limit 85 to (letter or historical article or comment or editorial or news or case reports) (4)
87 85 not 86 (122)

Database: Medline epubs ahead of print

Platform: Ovid

Version: Ovid MEDLINE(R) Epub Ahead of Print <July 17, 2020>

Search date: 21 July 2020

Number of results retrieved: 32

Search strategy:

Database: Ovid MEDLINE(R) Epub Ahead of Print <July 17, 2020>

Search Strategy:

1 Gender Dysphoria/ (0)
2 Gender Identity/ (0)
3 "Sexual and Gender Disorders"/ (0)
4 Transsexualism/ (0)
5 Transgender Persons/ (0)
6 Health Services for Transgender Persons/ (0)
7 exp Sex Reassignment Procedures/ (0)
8 (gender* adj3 (dysphori* or incongru* or identi* or disorder* or confus* or minorit* or
queer*)).tw. (430)
9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or
transmen* or transperson* or transpeopl*).tw. (637)
10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw.
(1499)
11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (179)
12 (male-to-female or m2f or female-to-male or f2m).tw. (2460)

13 or/1-12 (4883)
 14 exp Infant/ or Infant Health/ or Infant Welfare/ (0)
 15 (prematu* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born*
 or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn.
 (15416)
 16 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (0)
 17 Minors/ (0)
 18 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (53285)
 19 exp pediatrics/ (0)
 20 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (22649)
 21 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (0)
 22 Puberty/ (0)
 23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert*
 or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn.
 (13005)
 24 Schools/ (0)
 25 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (0)
 26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or
 pupil* or student*).ti,ab,jn. (12420)
 27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen"
 or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or
 aged)).ti,ab. (1407)
 28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19")
 adj2 (year or years or age or ages or aged)).ti,ab. (20083)
 29 or/14-28 (87968)
 30 13 and 29 (1618)
 31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw.
 (1)
 32 30 or 31 (1618)
 33 Hormones/ad, tu, th (0)
 34 exp Progesterone/ad, tu, th (0)
 35 exp Estrogens/ad, tu, th (0)
 36 exp Gonadal Steroid Hormones/ad, tu, th (0)
 37 (progesteron* or oestrogen* or estrogen*).tw. (1876)
 38 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or
 treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)).tw. (63)
 39 exp Estradiol/ad, tu, th (0)
 40 exp Testosterone/ad, tu, th (0)
 41 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or
 testocaps* or nebido or testavan).tw. (846)
 42 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylestrad* or elleste or
 progynova or zumenon or bedol or femseven or nuvelle).tw. (665)
 43 or/33-42 (2850)
 44 32 and 43 (64)
 45 limit 44 to yr="2000 -Current" (61)
 46 animals/ not humans/ (0)
 47 45 not 46 (61)
 48 limit 47 to english language (61)
 49 (MEDLINE or pubmed).tw. (7948)
 50 systematic review.tw. (7508)
 51 systematic review.pt. (28)
 52 meta-analysis.pt. (37)
 53 intervention\$.ti. (4267)
 54 or/49-53 (15048)
 55 randomized controlled trial.pt. (1)

56 randomi?ed.mp. (14113)
57 placebo.mp. (3097)
58 or/55-57 (15128)
59 exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation
studies as topic/ or exp statistics as topic/ (34)
60 ((control and (group* or study)) or (time and factors)).mp. (31615)
61 (program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-
up*).mp. (65735)
62 or/59-61 (88222)
63 Observational Studies as Topic/ (0)
64 Observational Study/ (4)
65 Epidemiologic Studies/ (0)
66 exp Case-Control Studies/ (0)
67 exp Cohort Studies/ (0)
68 Cross-Sectional Studies/ (0)
69 Controlled Before-After Studies/ (0)
70 Historically Controlled Study/ (0)
71 Interrupted Time Series Analysis/ (0)
72 Comparative Study.pt. (0)
73 case control\$.tw. (2577)
74 case series.tw. (2480)
75 (cohort adj (study or studies)).tw. (7959)
76 cohort analy\$.tw. (287)
77 (follow up adj (study or studies)).tw. (632)
78 (observational adj (study or studies)).tw. (3763)
79 longitudinal.tw. (7079)
80 prospective.tw. (12148)
81 retrospective.tw. (16600)
82 cross sectional.tw. (9459)
83 or/63-82 (48534)
84 54 or 58 or 62 or 83 (119752)
85 48 and 84 (32)
86 limit 85 to (letter or historical article or comment or editorial or news or case reports) (0)
87 85 not 86 (32)

Database: Medline daily update

Platform: Ovid

Version: Ovid MEDLINE(R) Daily Update <July 21, 2020>

Search date: 22 July 2020

Number of results retrieved: 3

Search strategy

Database: Ovid MEDLINE(R) Daily Update <July 21, 2020>

Search Strategy:

1 Gender Dysphoria/ (4)
2 Gender Identity/ (38)
3 "Sexual and Gender Disorders"/ (0)
4 Transsexualism/ (2)
5 Transgender Persons/ (26)
6 Health Services for Transgender Persons/ (1)
7 exp Sex Reassignment Procedures/ (3)
8 (gender* adj3 (dysphori* or incongru* or identi* or disorder* or confus* or minorit* or
queer*)).tw. (22)

9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (39)

10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (87)

11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (15)

12 (male-to-female or m2f or female-to-male or f2m).tw. (181)

13 or/1-12 (358)

14 exp Infant/ or Infant Health/ or Infant Welfare/ (932)

15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (981)

16 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (1756)

17 Minors/ (3)

18 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (3672)

19 exp pediatrics/ (75)

20 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (1658)

21 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (2006)

22 Puberty/ (8)

23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (732)

24 Schools/ (56)

25 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (5)

26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (622)

27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (98)

28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (1301)

29 or/14-28 (6705)

30 13 and 29 (130)

31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (0)

32 30 or 31 (130)

33 Hormones/ad, tu, th (3)

34 exp Progesterone/ad, tu, th (3)

35 exp Estrogens/ad, tu, th (8)

36 exp Gonadal Steroid Hormones/ad, tu, th (22)

37 (progesteron* or oestrogen* or estrogen*).tw. (161)

38 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)).tw. (3)

39 exp Estradiol/ad, tu, th (8)

40 exp Testosterone/ad, tu, th (8)

41 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or testocaps* or nebido or testavan).tw. (79)

42 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylestrad* or elleste or progynova or zumenon or bedol or femseven or nuvelle).tw. (61)

43 or/33-42 (261)

44 32 and 43 (7)

45 limit 44 to yr="2000 -Current" (7)

46 animals/ not humans/ (3647)

47 45 not 46 (6)

48 limit 47 to english language (6)

49 (MEDLINE or pubmed).tw. (529)

50 systematic review.tw. (512)

- 51 systematic review.pt. (522)
- 52 meta-analysis.pt. (370)
- 53 intervention\$.ti. (247)
- 54 or/49-53 (1065)
- 55 randomized controlled trial.pt. (595)
- 56 randomi?ed.mp. (1203)
- 57 placebo.mp. (219)
- 58 or/55-57 (1234)
- 59 exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/ (7958)
- 60 ((control and (group* or study)) or (time and factors)).mp. (4307)
- 61 (program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-up*).mp. (5828)
- 62 or/59-61 (11814)
- 63 Observational Studies as Topic/ (27)
- 64 Observational Study/ (449)
- 65 Epidemiologic Studies/ (7)
- 66 exp Case-Control Studies/ (2173)
- 67 exp Cohort Studies/ (3287)
- 68 Cross-Sectional Studies/ (837)
- 69 Controlled Before-After Studies/ (1)
- 70 Historically Controlled Study/ (0)
- 71 Interrupted Time Series Analysis/ (6)
- 72 Comparative Study.pt. (768)
- 73 case control\$.tw. (182)
- 74 case series.tw. (139)
- 75 (cohort adj (study or studies)).tw. (561)
- 76 cohort analy\$.tw. (22)
- 77 (follow up adj (study or studies)).tw. (40)
- 78 (observational adj (study or studies)).tw. (253)
- 79 longitudinal.tw. (429)
- 80 prospective.tw. (778)
- 81 retrospective.tw. (1032)
- 82 cross sectional.tw. (739)
- 83 or/63-82 (5471)
- 84 54 or 58 or 62 or 83 (12581)
- 85 48 and 84 (3)
- 86 limit 85 to (letter or historical article or comment or editorial or news or case reports) (0)
- 87 85 not 86 (3)

Database: Embase

Platform: Ovid
 Version: Embase <1974 to 2020 July 22>
 Search date: 23 July 2020
 Number of results retrieved: 1207
 Search strategy:

Database: Embase <1974 to 2020 July 22>
 Search Strategy:

-
- 1 exp Gender Dysphoria/ (5399)
 - 2 Gender Identity/ (16820)
 - 3 "Sexual and Gender Disorders"/ (24689)
 - 4 Transsexualism/ (3869)
 - 5 exp Transgender/ (6597)

6 Health Services for Transgender Persons/ (158848)
7 exp Sex Reassignment Procedures/ (1108)
8 (gender* adj3 (dysphori* or incongru* or identi* or disorder* or confus* or minorit* or
9 queer*)),.tw. (12470)
10 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or
11 transmen* or transperson* or transpeopl*).tw. (22509)
12 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw.
13 (154446)
14 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)),.tw. (10327)
15 (male-to-female or m2f or female-to-male or f2m).tw. (200166)
16 or/1-12 (581748)
17 exp juvenile/ or Child Behavior/ or Child Welfare/ or Child Health/ or infant welfare/ or
18 "minor (person)"/ or elementary student/ or adolescent health/ or middle school student/ or
19 high school student/ (3440943)
20 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born*
21 or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn.
22 (1186161)
23 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (3586795)
24 exp pediatrics/ (106214)
25 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (1491597)
26 exp adolescence/ or exp adolescent behavior/ or adolescent health/ or high school
27 student/ or middle school student/ (105108)
28 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert*
29 or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn.
30 (641660)
31 school/ or high school/ or kindergarten/ or middle school/ or primary school/ or nursery
32 school/ or day care/ (103791)
33 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or
34 pupil* or student*).ti,ab,jn. (687437)
35 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen"
36 or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or
37 aged)).ti,ab. (138908)
38 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19")
39 adj2 (year or years or age or ages or aged)).ti,ab. (1562903)
40 or/14-24 (7130881)
41 13 and 25 (181778)
42 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw.
43 (17)
44 26 or 27 (181778)
45 hormone/bd, ad, an, cr, do, it, dt, to, ei, ih, ia, ar, cv, dl, im, na, ip, ut, va, iv, ve, vi, po,
46 pa, pr, sc, li, th, tp, td (5160)
47 exp progesterone derivative/bd, ad, an, cr, do, it, dt, to, ei, ih, ia, ar, cv, dl, im, na, ip,
48 ut, va, iv, ve, vi, po, pa, pr, sc, li, th, tp, td (23479)
49 exp estrogen/bd, ad, an, cr, do, it, dt, to, ei, ih, ia, ar, cv, dl, im, na, ip, ut, va, iv, ve, vi,
50 po, pa, pr, sc, li, th, tp, td (57641)
51 steroid hormone/bd, ad, an, cr, do, it, dt, to, ei, ih, ia, ar, cv, dl, im, na, ip, ut, va, iv, ve,
52 vi, po, pa, pr, sc, li, th, tp, td (372)
53 sex hormone/bd, ad, an, cr, do, it, dt, to, ei, ih, ia, ar, cv, dl, im, na, ip, ut, va, iv, ve, vi,
54 po, pa, pr, sc, li, th, tp, td (1984)
55 hormonal therapy/ (42222)
56 (progesteron* or oestrogen* or estrogen*).tw. (254142)
57 ((cross-sex or crossex or gender-affirm*) and (hormon* or steroid* or therap* or
58 treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)).tw. (1224)
59 exp estradiol derivative/bd, ad, an, cr, do, it, dt, to, ei, ih, ia, ar, cv, dl, im, na, ip, ut, va,
60 iv, ve, vi, po, pa, pr, sc, li, th, tp, td (30740)

38 exp testosterone derivative/bd, ad, an, cr, do, it, dt, to, ei, ih, ia, ar, cv, dl, im, na, ip, ut,
 va, iv, ve, vi, po, pa, pr, sc, li, th, tp, td (15868)
 39 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or
 testocaps* or nebido or testavan).tw. (99596)
 40 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylesttrad* or elleste or
 progynova or zumenon or bedol or femseven or nuvelle).tw. (114290)
 41 or/29-40 (438737)
 42 28 and 41 (6053)
 43 limit 42 to yr="2000 -Current" (4741)
 44 nonhuman/ not human/ (4649157)
 45 43 not 44 (3636)
 46 limit 45 to english language (3513)
 47 (MEDLINE or pubmed).tw. (261145)
 48 exp systematic review/ or systematic review.tw. (302985)
 49 meta-analysis/ (191173)
 50 intervention\$.ti. (200041)
 51 or/47-50 (660206)
 52 random:.tw. (1552336)
 53 placebo:.mp. (455979)
 54 double-blind:.tw. (210671)
 55 or/52-54 (1807280)
 56 cohort analysis/ (596360)
 57 exp epidemiology/ (3434332)
 58 exp clinical trial/ (1504711)
 59 evaluation study/ (45870)
 60 statistics/ (301181)
 61 ((control and (group* or study)) or (time and factors)).mp. (3324555)
 62 (program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-
 up*).mp. (6067112)
 63 or/56-62 (11048972)
 64 Clinical study/ (155444)
 65 Case control study/ (157943)
 66 Family study/ (26047)
 67 Longitudinal study/ (141660)
 68 Retrospective study/ (937696)
 69 comparative study/ (859061)
 70 Prospective study/ (613138)
 71 Randomized controlled trials/ (182542)
 72 70 not 71 (606604)
 73 Cohort analysis/ (596360)
 74 cohort analy\$.tw. (13020)
 75 (Cohort adj (study or studies)).tw. (302159)
 76 (Case control\$ adj (study or studies)).tw. (137432)
 77 (follow up adj (study or studies)).tw. (63423)
 78 (observational adj (study or studies)).tw. (168428)
 79 (epidemiologic\$ adj (study or studies)).tw. (106448)
 80 (cross sectional adj (study or studies)).tw. (220073)
 81 case series.tw. (104089)
 82 prospective.tw. (861922)
 83 retrospective.tw. (886445)
 84 or/64-69,72-83 (4047788)
 85 51 or 55 or 63 or 84 (12494560)
 86 46 and 85 (2151)
 87 86 not (letter or editorial).pt. (2137)

88 87 not (conference abstract or conference paper or conference proceeding or "conference review").pt. (1207)

Database: APA PsycInfo

Platform: Ovid
Version: APA PsycInfo <1806 to July Week 2 2020>
Search date: 22 July 2020
Number of results retrieved: 581
Search strategy:

Database: APA PsycInfo <1806 to July Week 2 2020>
Search Strategy:

-
- 1 Gender Dysphoria/ (936)
 - 2 Gender Identity/ (8648)
 - 3 Transsexualism/ (2825)
 - 4 Transgender/ (5257)
 - 5 exp Gender Reassignment/ (568)
 - 6 (gender* adj3 (dysphori* or incongruen* or identi* or disorder* or confus* or minorit* or queer*)).tw. (15276)
 - 7 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (13028)
 - 8 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (7679)
 - 9 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (5796)
 - 10 (male-to-female or m2f or female-to-male or f2m).tw. (63688)
 - 11 or/1-10 (99498)
 - 12 exp Infant Development/ (21841)
 - 13 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (150219)
 - 14 Child Characteristics/ or exp Child Behavior/ or Child Psychology/ or exp Child Welfare/ or Child Psychiatry/ (23423)
 - 15 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (984230)
 - 16 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (78962)
 - 17 Adolescent Psychiatry/ or Adolescent Behavior/ or Adolescent Development/ or Adolescent Psychology/ or Adolescent Characteristics/ or Adolescent Health/ (62142)
 - 18 Puberty/ (2753)
 - 19 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (347604)
 - 20 Schools/ (29181)
 - 21 Child Day Care/ or Nursery Schools/ (2836)
 - 22 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (772814)
 - 23 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (21475)
 - 24 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (285697)
 - 25 or/12-24 (1765408)
 - 26 11 and 25 (49560)
 - 27 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (14)

28 26 or 27 (49561)
 29 hormones/ (8408)
 30 sex hormones/ (1777)
 31 exp progestational hormones/ (2409)
 32 estrogens/ (3889)
 33 steroids/ (3797)
 34 (progesteron* or oestrogen* or estrogen*).tw. (11188)
 35 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)).tw. (457)
 36 estradiol/ (3120)
 37 testosterone/ (5606)
 38 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or testocaps* or nebido or testavan).tw. (9625)
 39 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylestrad* or elleste or progynova or zumenon or bedol or femseven or nuvelle).tw. (6741)
 40 or/29-39 (30344)
 41 28 and 40 (1005)
 42 limit 41 to yr="2000 -Current" (749)
 43 limit 42 to english language (692)
 44 limit 43 to ("0200 book" or "0240 authored book" or "0280 edited book" or "0300 encyclopedia" or "0400 dissertation abstract") (111)
 45 43 not 44 (581)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); CENTRAL

Platform: Wiley

Version:

CDSR –Issue 7 of 12, July 2020

CENTRAL – Issue 7 of 12, July 2020

Search date: 22 July 2020

Number of results retrieved: CDSR 0 ; CENTRAL 67.

ID	SearchHits
#1	MeSH descriptor: [Gender Dysphoria] this term only 3
#2	MeSH descriptor: [Gender Identity] this term only 227
#3	MeSH descriptor: [Sexual and Gender Disorders] this term only 2
#4	MeSH descriptor: [Transsexualism] this term only 27
#5	MeSH descriptor: [Transgender Persons] this term only 36
#6	MeSH descriptor: [Health Services for Transgender Persons] this term only 0
#7	MeSH descriptor: [Sex Reassignment Procedures] explode all trees 4
#8	(gender* near/3 (dysphori* or incongru* or identi* or disorder* or confus* or minorit* or queer*)):ti,ab,kw 702
#9	(transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*):ti,ab,kw 959
#10	(trans or crossgender* or cross-gender* or crosssex* or cross-sex* or genderqueer*):ti,ab,kw 3969
#11	((sex or gender*) near/3 (reassign* or chang* or transform* or transition*)):ti,ab,kw 524
#12	(male-to-female or m2f or female-to-male or f2m):ti,ab,kw 516
#13	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 6413
#14	MeSH descriptor: [Infant] explode all trees 28440
#15	MeSH descriptor: [Infant Health] this term only 49
#16	MeSH descriptor: [Infant Welfare] this term only 82

#17 (prematu* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*):ti,ab,kw,so 89530

#18 MeSH descriptor: [Child] explode all trees 44089

#19 MeSH descriptor: [Child Behavior] explode all trees 2061

#20 MeSH descriptor: [Child Health] this term only 98

#21 MeSH descriptor: [Child Welfare] this term only 325

#22 MeSH descriptor: [Minors] this term only 8

#23 (child* or minor or minors or boy* or girl* or kid or kids or young*):ti,ab,kw,so 265417

#24 MeSH descriptor: [Pediatrics] explode all trees 661

#25 (pediatric* or paediatric* or peadiatric*):ti,ab,kw,so 57725

#26 MeSH descriptor: [Adolescent] this term only 102154

#27 MeSH descriptor: [Adolescent Behavior] this term only 1358

#28 MeSH descriptor: [Adolescent Health] this term only 29

#29 MeSH descriptor: [Puberty] this term only 295

#30 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*):ti,ab,kw,so 140927

#31 MeSH descriptor: [Schools] this term only 1914

#32 MeSH descriptor: [Child Day Care Centers] this term only 231

#33 MeSH descriptor: [Nurseries, Infant] explode all trees 17

#34 MeSH descriptor: [Schools, Nursery] this term only 37

#35 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*):ti,ab,kw,so 97810

#36 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") near/2 (year or years or age or ages or aged)):ti,ab 6710

#37 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") near/2 (year or years or age or ages or aged)):ti,ab 196881

#38 #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 516067

#39 #13 and #38 2488

#40 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*):ti,ab,kw 0

#41 #39 or #40 2488

#42 MeSH descriptor: [Hormones] this term only 2241

#43 MeSH descriptor: [Progesterone] explode all trees 3135

#44 MeSH descriptor: [Estrogens] explode all trees 1841

#45 MeSH descriptor: [Gonadal Steroid Hormones] explode all trees 10747

#46 (progesteron* or oestrogen* or estrogen*):ti,ab,kw 18387

#47 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or treatment* or prescri* or pharm* or medic* or drug* or intervention* or care)):ti,ab,kw 24

#48 MeSH descriptor: [Estradiol] explode all trees 4434

#49 MeSH descriptor: [Testosterone] explode all trees 2945

#50 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or testocaps* or nebido or testavan):ti,ab,kw 7386

#51 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylestrad* or elleste or progynova or zumenon or bedol or femseven or nuvelle):ti,ab,kw 11410

#52 #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 31870

#53 #41 and #52 121

#54 "conference":pt or (clinicaltrials or trialsearch):so 492465

#55 #53 not #54 72

Database: HTA

Platform: Wiley
 Version: up to 2018
 Search date: 22nd July 2020
 Number of results retrieved: 4
 Search strategy:

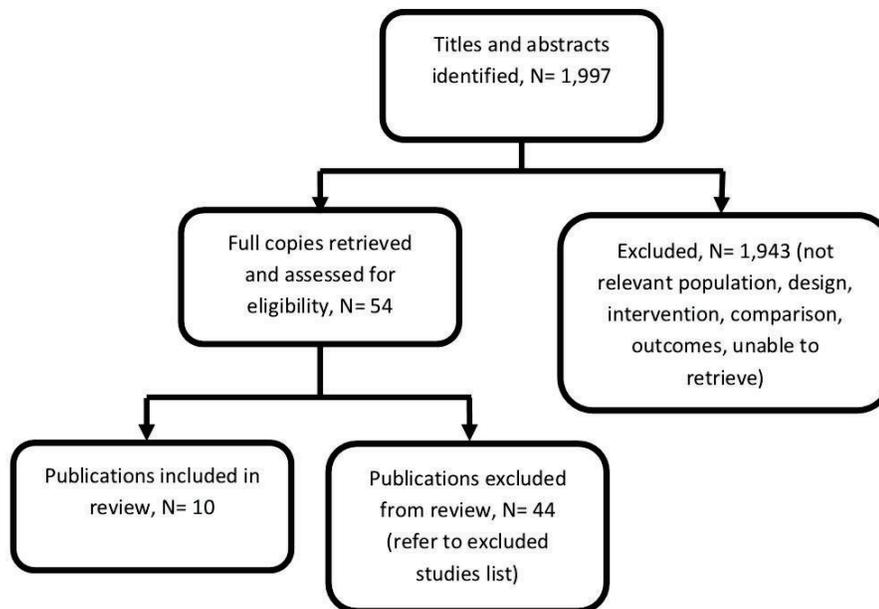
#1 MeSH DESCRIPTOR Gender Dysphoria 0
 #2 MeSH DESCRIPTOR Gender Identity 12
 #3 MeSH DESCRIPTOR Sexual and Gender Disorders 2
 #4 MeSH DESCRIPTOR Transsexualism 12
 #5 MeSH DESCRIPTOR Transgender Persons 3
 #6 MeSH DESCRIPTOR Health Services for Transgender Persons 0
 #7 MeSH DESCRIPTOR Sex Reassignment Procedures EXPLODE ALL TREES 1
 #8 ((gender* near3 (dysphori* or incongru* or identi* or disorder* or confus* or minorit* or queer*))) 28
 #9 ((transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*)) 76
 #10 ((trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*)) 83
 #11 (((sex or gender*) near3 (reassign* or chang* or transform* or transition*))) 24
 #12 ((male-to-female or m2f or female-to-male or f2m)) 86
 #13 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 261
 #14 MeSH DESCRIPTOR Infant EXPLODE ALL TREES 2964
 #15 MeSH DESCRIPTOR Infant Health 0
 #16 MeSH DESCRIPTOR Infant Welfare 22
 #17 ((prematu* or pre-matur* or preterm* or pre-term* or infan* or newborn* or newborn* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*)) 5510
 #18 MeSH DESCRIPTOR Child EXPLODE ALL TREES 4935
 #19 MeSH DESCRIPTOR Child Behavior EXPLODE ALL TREES 64
 #20 MeSH DESCRIPTOR Child Health 2
 #21 MeSH DESCRIPTOR Child Welfare 80
 #22 MeSH DESCRIPTOR Minors 2
 #23 ((child* or minor or minors or boy* or girl* or kid or kids or young*)) 13575
 #24 MeSH DESCRIPTOR Pediatrics EXPLODE ALL TREES 119
 #25 ((pediatric* or paediatric* or peadiatric*)) 2842
 #26 MeSH DESCRIPTOR Adolescent 4594
 #27 MeSH DESCRIPTOR Adolescent Behavior 94
 #28 MeSH DESCRIPTOR Adolescent Health 0
 #29 MeSH DESCRIPTOR Puberty 3
 #30 ((adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*)) 5621
 #31 MeSH DESCRIPTOR Schools 168
 #32 MeSH DESCRIPTOR Child Day Care Centers 12
 #33 MeSH DESCRIPTOR Schools, Nursery 3
 #34 ((pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*)) 4454
 #35 (((("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") near2 (year or years or age or ages or aged))) 380
 #36 (((("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") near2 (year or years or age or ages or aged)))) 7996

#37 #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 22640
 #38 #13 AND #37 116
 #39 (#13 AND #37) IN HTA 4

Appendix C Evidence selection

The literature searches identified 1,997 references. These were screened using their titles and abstracts and 54 references were obtained and assessed for relevance. Of these, 10 references are included in the evidence review. The remaining 44 references were excluded and are listed in [appendix D](#).

Figure 1 – Study selection flow diagram



References submitted with Preliminary Policy Proposal

There is no preliminary policy proposal for this policy.

Appendix D Excluded studies table

Study reference	Reason for exclusion
Aranda G, Mora M, Hanzu FA et al. (2019) Effects of sex steroids on cardiovascular risk profile in transgender men under gender affirming hormone therapy. <i>Endocrinologia, diabetes y nutricion</i> 66(6): 385–392	Excluded on population – adult study, participants not 18 years or less (mean age 27.1 years).
Arnold, Justin D, Sarkodie, Eleanor P, Coleman, Megan E et al. (2016) Incidence of Venous Thromboembolism in Transgender Women	Excluded on population – adult study, participants not 18 years or less (mean age 33.2 years).

Study reference	Reason for exclusion
Receiving Oral Estradiol. The journal of sexual medicine 13(11): 1773–1777	
Asscheman, Henk, Giltay, Erik J, Megens, Jos A J et al. (2011) A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. European journal of endocrinology 164(4): 635–42	Excluded on population – although some participants started gender-affirming hormones when young, the study does not report the proportion who started treatment when 18 years or less. Mean ages at start of treatment were 31.4 years (transfemales) and 26.1 years (transmales), suggesting the majority of participants were older than 18 years at the start of treatment. Outcomes not reported separately for people aged 18 years or less.
Author not, found (2014) Hormone therapy for the treatment of gender dysphoria. Lansdale, PA: HAYES, Inc	Full text paper not available.
Baba, T., Endo, T., Honnma, H. et al. (2007) Association between polycystic ovary syndrome and female-to-male transsexuality. Human Reproduction 22(4): 1011–1016	Excluded on population – although study included some younger people (age range 17 to 47), most participants were adults (mean age around 25 years) and the proportion who started treatment when 18 years or less is not reported. Outcomes not reported separately for people aged 18 years or less.
Becerra-Fernandez A, Perez-Lopez G, Roman MM et al. (2014) Prevalence of hyperandrogenism and polycystic ovary syndrome in female to male transsexuals. Endocrinologia y Nutricion: Organo de la Sociedad Espanola de Endocrinologia y Nutricion 61(7): 351–8	Excluded on population – although study included some younger people (age range 18 to 45), most participants were adults (mean age around 25 years) and the proportion who started treatment when 18 years or less is not reported. Outcomes not reported separately for people aged 18 years or less.
Becker I, Auer M, Barkmann C et al. (2018) A Cross-Sectional Multicenter Study of Multidimensional Body Image in Adolescents and Adults with Gender Dysphoria Before and After Transition-Related Medical Interventions. Archives of Sexual Behavior 47(8): 2335–2347	Excluded on population – study included people aged 14 to 21 years. Outcomes not reported separately for people aged 18 years or less. Better evidence available – only 11 participants received gender-affirming hormones. The majority of the study cohort were either pre-treatment, received puberty suppression alone, or received hormones and underwent surgery.
Chew D, Anderson J, Williams K et al. (2018) Hormonal Treatment in Young People With Gender Dysphoria: A Systematic Review. Pediatrics 141(4): e20173742	Excluded on better available evidence - systematic review did not meta-analyse results from. Individual studies from this systematic review are either